R E M A R K S

Telephone Interview with the Examiner

The undersigned had a telephone discussion with Examiner Staples on February 3, 2010 concerning the January 29, 2010 Office Action. The following issues were discussed during said telephone interview.

1. Examiner Staples said that it may be possible to avoid the 35 USC 103 rejections set forth in the January 29, 2010 Office Action by amending the rejected claims 1 to 4 and 12 to 14 to be similar to the claimed subject matter in the allowable kit claims 15 to 17.

2. Examiner Staples suggested that the first six lines of claims 1 and 2 be amended as follows:

> "An oligonucleotide used as a primer ~~comprising~~ consisting of:
>
> (a) a 2'-O,4'-C-ethylene nucleotide (ENA) unit which is the third nucleotide from the 3'-end of the oligonucleotide, wherein the other nucleotides are natural nucleotides and wherein the nucleotide at the 3'-end is defined as the first nucleotide[[,]] ~~and the other nucleotides are natural nucleotides~~;"

Claim Amendments

Claims 1 and 2 were amended following Examiner Staples' suggestions discussed hereinabove and in item no. 8 on page 4 of the January 29, 2010 Office Action.

Following the Examiner's suggestion in item no. 8 on page 4 of the January 29, 2010 Office Action, claim 3, line 2 and claim 4, line 2 were amended to replace "comprising" with --consisting of--.

Claims 12 to 14 were editorially revised in reply to item no. 9 bridging pages 4 to 5 of the January 29, 2010 Office Action.

Allowable Subject Matter

Applicant is pleased to note that in item no. 16 at the bottom of page 26 of the January 29, 2010 Office Action, it was stated that claims 15 to 17 are allowed.

In item no. 17 at the bottom of page 26 of the January 29, 2010 Office Action, it was stated that claim 19 would be allowable if it did not depend on claims 12 to 14.

Claim Interpretation

1. In item no. 8 on page 4 of the January 29, 2010 Office Action, the Examiner provided his interpretation of claims 1 to 4

that parts (a), (b) and (c) are added one to another. It was stated that parts (a) and (b) are not natural nucleotides and thus can be modified nucleotides which include ENA and LNA nucleotides. It was further stated that th term "comprises" encompasses additional nucleotides other than those recited in parts (a), (b) and (c). The Examiner concluded that the claimed primers can contain an ENA in the fourth position and positions inward from the 3'-end and may further comprises natural and modified nucleotides.

By amending claims 1 to 4 to replace "comprising" with --consisting of--, it is clear that applicant's presently claimed primers include an ENA unit only at the third position from 3'-end. Therefore, the claimed primers do not contain an ENA in the fourth position and inward from the 3'-end.

2. In item no. 9 bridging pages 4 to 5 of the January 29, 2010 Office Action, the Examiner provided his interpretation of kit claims 12 to 14.

In view of the above amendments to claims 12 to 14, it is clear that claims 12 to 14 do not encompass oligonucleotides where the first and the third nucleotides are ENA.

Data Regarding ENA at the Third Position From the 3'-End

In item no. 10 at the middle of page 5 of the January 29, 2010 Office Action, the Examiner's commented on the data regarding ENA versus LNA substituted at the third position in the REMARKS set forth in the AMENDMENT UNDER 37 CFR 1.116 filed December 28, 2009 in the DECLARATION UNDER 37 CFR 1.132 of Makoto KOIZUMI dated January 23, 2009 (which was filed in the USPTO on February 2, 2009).

As discussed above, applicant's present claims 1 to 14 specify an ENA unit of the primers at the third position from the 3'-end.

Obviousness Rejections Under 35 USC 103

1. Claims 1 to 4, 23, 29 and 41 were rejected under 35 USC 103 as being unpatentable over Kaneko et al. (US 2002/0147332), Morita et al., Braasch et al. and Orum et al. for the reasons set forth in item no. 13 at the middle of page 6 and continuing to page 13 of the January 29, 2010 Office Action.

It was admitted at the bottom of page 7 of the January 29, 2010 Office Action that Kaneko et al. do not teach that the fourth nucleotide from the 3'-end is an ENA unit.

It was admitted at the bottom of page 8 in the January 29, 2010 Office Action that regarding claims 1, 2, 5, 23 and 29,

Morita et al. (i) do not specifically teach the intended use of nucleotides complementary to a gene which is a target, a target gene; and (ii) do not specifically teach a mutant nucleotide.

It was admitted on page 10 of the January 29, 2010 Office Action that regarding claims 1 to 5, Braasch et al. and Orum et al. do not specifically teach an ENA unit and to not specifically teach all the limitations and intended uses of the claimed oligonucleotides in a single oligonucleotide.

It was admitted on page 11 of the January 29, 2010 Office Action that regarding claims 1 to 4, Morita et al. do not specifically teach an ENA at the third position from the 3'-end.

This rejection is based on the interpretation that applicant's rejected claims encompass primers with at least one ENA at the fourth position from the 3'-end and other ENA and LNA substitutions.

It is respectfully submitted that the cited references do not teach or suggest primers which have an ENA unit only at the third position from the 3'-end and do not disclose or suggest the specific results provided by the primers of the presently claimed invention.

Applicant's presently claimed invention clearly sets forth the position and the number of the ENA, i.e., the ENA unit is only at the third nucleotide from the 3'-end of the oligonucleotide. In contrast thereto, in claim 84 of Kaneko et al., there is no limitation for the number, the position and the structure of oligonucleotide units. As shown in Fig. 5 to Fig. 7 of the above-identified application, the specific detection for gene polymorphisms described in the above-identified application was achieved by using a primer claimed in the above-identified application (an ENA only at the third nucleotide from the 3'-end). Therefore, it is respectfully submitted that based on Kaneko et al., a person of ordinary skill in the art would not be able to arrive at the structure of the primer of the presently claimed invention and would not be able to predict the properties thereof. Furthermore, it is respectfully submitted that based on Kaneko et al., a person of ordinary skill in the are would not be able to arrive at applicant's presently claimed invention.

The argument in the preceding paragraph is also applicable for claims 62, 72, 78, 84, 92, 96 and 102, and paragraphs [0016], [0089] and [[9172] of Kaneko et al.

Braasch et al. disclose many kinds of oligonucleotides having an LNA at various positions and do not particularly specify the position of the LNA. In addition, the oligonucleotide is made for detecting the Tm value, and not for detecting SNPs (single nucleotide polymorphisms).

There is no specific teaching in Braasch et al. concerning inserting a LNA (let alone an ENA) at the third position from the 3'-end of an oligonucleotide.

Orum et al. show the thermostability of octamer oligonucleotides (Table 1). The length of these oligonucleotides are different from the presently claimed invention.

Braasch et al. and Orum et al. do not teach a nucleotide length (i.e., how many nucleotides are in the oligonucleotide?) of the oligonucleotide and where and how many LNAs should be inserted in the oligonucleotide to obtain a oligonucleotide which can detect SNPs.

It is therefore respectfully submitted that Braasch et al. and Orum et al. are completely different from the presently claimed invention.

2. Claims 12 to 14, 19 and 52 to 54 were rejected under 35 USC 103 as being unpatentable over Kaneko et al. (US 2002/0147332), Morita et al., Braasch et al., Orum et al. and

Weston et al. (USP 6,391,593) for the reasons set forth in item no. 14 beginning at the bottom of page 13 and continuing to the middle of page 25 of the January 29, 2010 Office Action.

It was admitted at the top of page 16 of the January 29, 2010 Office Action that Morita et al. do not specifically teach an ENA unit at the third position from the 3'-end.

It was admitted near the bottom of page 22 of the January 29, 2010 Office Action that Kaneko et al. do not specifically teach an oligonucleotide comprising an ENA unit at the third position from the 3'-end.

This rejection is based on the interpretation that claims 12 to 14 encompass primers with at least one ENA not only at the third position from the 3'-end, but also other positions.

Applicant's present claims 12 to 14 specify an ENA unit of primers at the third position fro the 3'-end.

For the reasons discussed hereinabove, it is respectfully submitted that applicant's claims 12 to 14 patentably distinguish over Kaneko et al., Morita et al., Braasch et al. and Orum et al.

Weston et al. do not specify the position and number of LNA units in their probes. In contrast thereto, applicant's claims specify the position (the third position) and number (one) of an ENA unit (the third nucleotide from the 3'-end thereof is a

2',4'-ethylene nucleotide (ENA) unit, wherein the nucleotide at the 3'-end is defined as the first nucleotide).

In addition, Weston et al. disclose a kit which comprises a following pair of probes:

(a) first probe: comprising a portion complementary to the sequence of interest and capable of hybridizing thereto, and a portion non-complementary to the sequence of interest;

(b) second probe: comprising a portion complementary to the sequence of interest and capable of hybridizing thereto, and a portion non-complementary to the sequence of interest, but complementary to that portion of the first probe which is non-complementary to the sequence of interest.

The structure of said pair of probes in Weston et al. is completely different from applicant's claims. It is therefore respectfully submitted that Weston et al. do not teach or suggest applicant's claimed kits.

It is therefore respectfully submitted that even if Weston et al. is added to the disclosures of Kaneko et al., Morita et al., Braasch et al. and Orum et al., applicant's present claims patentably distinguish over such combination of references.

3. Claims 20 to 22, 24 to 28, 30 to 40 and 42 to 43 were rejected under 35 USC 103 as being unpatentable over Kaneko et al. (US 2002/0147332), Morita et al., Braasch et al., Orum et al. as applied to claims 1 to 4, and further in view of Stanton, Jr. et al. (US 2001/0034023) for the reasons set forth in item no. 15 beginning at the middle of page 25 and continuing to the middle of page 26 of the January 29, 2010 Office Action.

It was admitted near the bottom of page 28 of the January 29, 2010 Office Action that Kaneko et al., Morita et al., Braasch et al. and Orum et al. do not teach the features of claims 20 to 22, 24 to 28, 30 to 40 ad 42 to 43.

Claims 20 to 22, 24 to 28, 30 to 40, 42 and 43 depend directly or indirectly on claims 1 to 4. Since it is respectfully submitted that applicant's present claims 1 to 4 patentably distinguish over the references discussed hereinabove, it follows that claims 20 to 22, 24 to 28, 30 to 40 and 42 and 43 are patentable.

For the reasons discussed hereinabove, it is respectfully submitted that applicant's present claims patentably distinguish over the disclosures of Kaneko et al., Morita et al., Braasch et al. and Orum et al. For the following reasons, adding the disclosure of Stanton, Jr. et al. to such combination of

references, does not deter from the patentability of applicant's present claims.

Stanton, Jr. et al. do not teach or suggest an oligonucleotide as recited in applicant's claims (the third nucleotide from the 3'-end thereof is a 2'-O,4'-ethylene nucleotide (ENA) unit, wherein the nucleotide at the 3'-end is defined as the first nucleotide) for detecting drug metabolizing genes.

Stanton, Jr. et al. do not disclose a method for identifying SNPs by using the oligonucleotides, as recited in applicant's presently claimed invention.

Withdrawal of each of the obviousness rejections is thus respectfully requested.

Evidence of Patentability of Applicant's Present Claims

Applicant has provided evidence that LNA substitution in the third position from the 3' end of the oligonucleotide would not have the same or a similar property as ENA substitution in the third position from the 3' end of the oligonucleotide. Applicant has also provided evidence rebutting the allegation that ENA substitution of LNA was known and obvious, prior to the presently claimed invention.

Oligonucleotides that have LNA in the third position from the 3'-end of the oligonucleotide are disclosed in the present specification (please see Reference Example 9 and Reference Example 10 on pages 73 and 74 of the present specification). In Reference Examples 9 and 10, the oligonucleotides have C^{e1p} in the third position from the 3' end. As noted in the last sentence on page 27 of the present specification, C^{e1p} is an LNA unit.

The advantageous results of an oligonucleotide having an ENA unit in the third position from the 3' end compared to an LNA unit in the third position in the 3' end is demonstrated by Test Example 1 beginning at the bottom of page 72 and continuing to page 82 of the present specification. Please see the discussion in the first and second paragraphs on page 82 of the present specification, which are reproduced as follows:

> "Figure 6 shows an example using Premix EX Taq (manufactured by Takara Shuzo Co., Ltd.) instead of Premix Taq (manufactured by Takara Shuzo Co., Ltd.). In this case also, when a primer wherein an ENA unit had been introduced into the third position from the 3'-end thereof was used, almost no non-complementary binding took place, and when the primer of Example 1 was used, the gene was amplified more efficiently and selectively.

> The fluorescence intensity of the detected band was converted into a numerical value, and it was then plotted, as shown in Figure 7. In the case of the compounds of Reference Examples 9 and 10, an LNA unit was introduced into the third position from the 3'-end thereof. When the compound of Reference Example 10 was used as the forward primer, 15% amplification of the gene due to non-complementary binding was observed. In contrast, when the compound of Example 2, wherein an ENA unit had been introduced into the third position from the 3'-end thereof, was used as a forward primer, only 6% amplification of the gene due to non-complementary binding was observed. Thus, it was revealed that such an ENA unit results in little non-complementary binding, having high selectivity."

Figures 6 and 7, which are discussed in the two preceding paragraphs, are reproduced as follows:

Figure 6

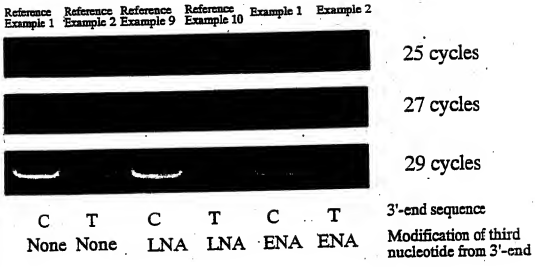
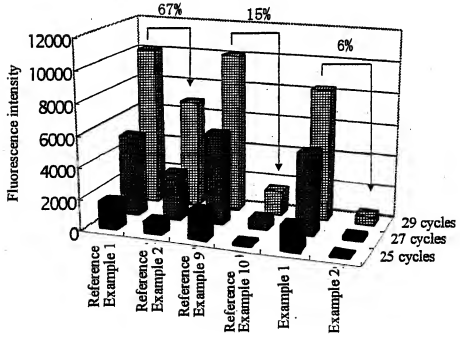


Figure 7



Figures 6 and 7 were explained in the paragraph bridging pages 8 and 9 of the DECLARATION UNDER 37 CFR 1.132 of Makoto KOIZUMI dated January 23, 2009. The aforesaid paragraph from the January 23, 2009 KOIZUMI DECLARATION is reproduced as follows:

> "Heretofore, a serious problem was that significant levels of mismatch extension from the 3' primer:template junction T:G is observed. As shown in Fig. 6 and 7 in the above-identified patent application, in the case of using DNA primers, mismatch extension from the 3' primer:template junction T:G was 67% of match extension from the 3' primer: template junction C:G. On the other hand, when a primer containing a LNA unit at the third position from the 3' end was used, the mismatch extension from the 3' primer: template junction T:G was 15% of match extension from the 3' primer:template junction C:G. Moreover, in the case of using ENA primers containing the ENA unit at the third position from the 3' end, mismatch extension from the 3' primer:template junction T:G decreased to only 6% of match extension from 3' primer:template junction C:G."

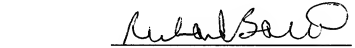
Rejoinder

If the claims of elected Group I are allowed, rejoinder and allowance of the withdrawn claims of non-elected Group II are respectfully requested (see item no. 3 on pages 4 to 5 o the November 5, 2007 Office Action).

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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